Networks in Biology and Neuroscience

CSE 5339: Topics in Network Data Analysis

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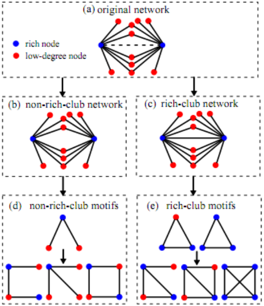
The Human Connectome - challenges and open problems

- The “connectome” refers to the complete set of neuronal connections of the brain [STK05]. To date, this dataset is incomplete.
- Motivation for studying the connectome: brain function is believed to be intrinsically tied to structural connectivity.

Example: Schizophrenia and network connectivity [vdHSC+13]

- van den Heuvel et al studied "rich-club organizations" in schizophrenic patients and healthy volunteers
- Results showed that the patients had an abnormally low number of rich-club connections between high degree hub nodes, which was linked to reduced overall communication capacity in the brain.



Challenge 0: Learning network terminology

Network concept	Network measure
Module	Degree
Hub	Strength
Core	Centrality
Rich club	Modularity

Formal definitions of these terms (and more) appear in [RS10]—as well as a Matlab toolbox and connectivity datasets to play with.

Challenge 1: The Need for a Multiscale View

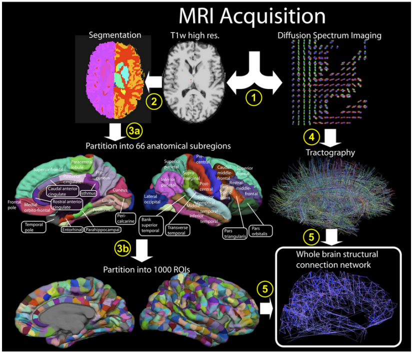
- Microscale: Subcellular compartments of individual neurons [BH10].
- Mesoscale: Neuronal populations and their interconnections [BWB$^+$09]
- Macroscale: Anatomically distinct brain regions
- At the microscale, things are fine, but the neuroscience community has not reached consensus on a way to “parcellate” the brain at larger scales.
- Among approximately 10^{11} neurons, there are only 10^{15} connections—resulting connectivity matrix is very sparse! Hence clustering techniques (and a large-scale viewpoint of the brain) are necessary [Spo12].

Example: A "Brain Mapping" project, from beginning to end

Hagmann et al [HCG+08] produced a seminal paper in 2008, describing their efforts towards "mapping" the brain.

- Data was extracted using noninvasive *diffusion imaging*
- Brain activation patterns recorded via fMRI
- Output: a *structural* network showing anatomical pathways, and a *functional* network showing interactions between active regions
- Network analysis tools: connectivity backbone, k-core decomposition, modularity detection, hub classification, node degree/strength/centrality/efficiency

Data extraction and network reconstruction



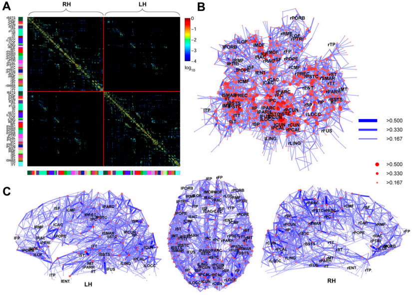
Idea: Begin with a mesh of $\sim$ 1000 volume elements to represent regions of the brain. Compute an "orientation distribution function" that captures "intensity of diffusion" in each direction. Calculated by integrating a density function along a unit vector w.r.t. radial measure.

Data extraction and network construction

Tractography: Used to compute diffusion curves. Idea: find local maxima of ODF, i.e. directions of maximum diffusion. Initialize "fibers" at randomly chosen points of the mesh, in the direction of the maximizers of the ODF. Extend fibers, attempting to reach maximizers at each step.

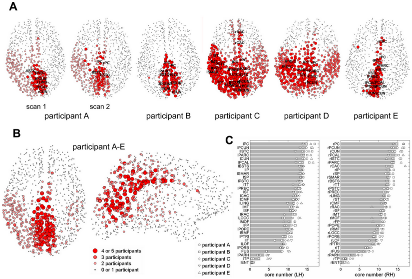
Network construction: Each of the 1000 regions becomes a node. Two nodes are connected by an edge if there is a fiber between them. Weight is assigned proportional to the connection density, along with some normalization factors.

Connectivity backbone



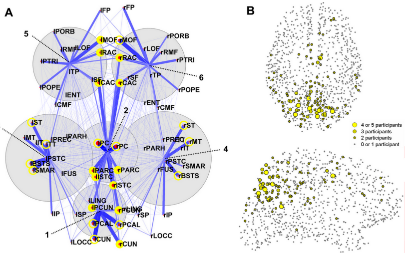
- Pick a maximal spanning tree, i.e. a spanning tree with maximal weight
- Add additional edges (sorted according to weight) until average node degree = ~ 4

k-core decomposition



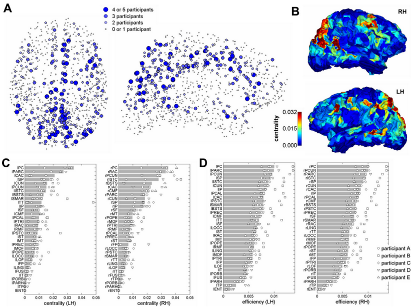
- The k-core is the largest subgraph whose nodes all have degree ≥ 4
- core number of a node = maximal k for which node belongs to the k-core
- k-core decomposition recursively removes nodes with the smallest core number

Modularity detection



- Modularity is a measure of the "community structure" of a network
- Interpretation: modularity is (up to a multiplicative constant) the number of edges between subsets, minus the expected number of edges between comparable subsets in a random network [New06].

Network degree/strength/centrality



- Node degree = column/row sum of a binary adjacency matrix
- Node strength = column/row sum of the adjacency matrix (w/ all weights)
- Node centrality (of node x) = fraction of all shortest paths between nodes s, t that pass through x

Challenge 2: Dealing with Individual Variations

- Even in the extremely simple connectome ($\sim$ 300 neurons) of *C. elegans*, individual variations are common [LPL+09].
- Significant differences are also noted in *Drosophila* (fly) brains [CSY+10].
- Not enough to study connectomics of individuals—need to study connectomics of populations.
- Idea: microscopic reconstructions of brain networks are difficult, clunky, and do not give complete insight into the network architecture. Instead, can we find a set of simple principles that can be used for a generative model?

Example: The trade-off between performance and energy [BS12]

- The brain is embedded in three-dimensional space of limited volume; as such, there are constraints on its wiring diagram.
- Brains are expensive to run, and there is a natural incentive to minimize its wiring cost. On the other hand, this cost needs to be balanced with the brain's performance.

Example: The trade-off between performance and energy [BS12]

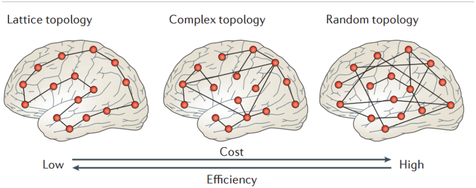


Figure: The network on the left is wired to minimize wiring cost–connections have short path lengths. But this does not favor communication between nodes that are physically far apart. The network on the right has direct connections even between nodes that are far apart, but the larger path lengths contribute a high wiring cost. Brain networks exhibit topology similar to the central network: there are clusters of nodes with short path lengths, as well as connector hubs that have short-cuts between distant brain regions.

Example: The trade-off between performance and energy [BS12]

- Several disorders appear to be associated to abnormal disruptions of this "brain network economy". It has been shown that Alzheimer's patients undergo a network reconfiguration that shifts towards greater clustering, greater path lengths, and reduced connections between hub nodes. Given that Alzheimer's manifests as dementia, this can be viewed as a shift towards decreased performance (but better energy savings) [YZL+10, LWC+10, SJN+07, HCE08].
- Multiple Sclerosis is a condition involving demyelination of axonal tracts, and the longest axonal tracts are most vulnerable to damage. Individuals with MS have been shown to exhibit reduced proportions of long-distance connections in their brain networks [HDC+09].

Challenge 3: Neural Plasticity

- Brains are constantly being rewired: at the microscale, cellular components are continually "refreshed" [PGB^{+}10], and at the macroscale, the neuronal architecture can (and does) undergo significant alterations over time [HS09].
- MRI and other imaging techniques only take snapshots–they do not fully capture the dynamics that occur over long timescales.
- Question: If neurons are dying and regenerating, how does memory persist? [DMFC12]
- Challenges abound, vast amounts of public data available—a rich field to mine.

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Questions?